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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,958	06/20/2000	Jihyun Francis Kim	19603/3286(CRF D-2062B)	5427

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/596,958	KIM ET AL.	
	Examiner	Art Unit	
	Annie R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 29-37* is/are pending in the application.

4a) Of the above claim(s) *32-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 29-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 June 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

1. Applicant's election with traverse of Group I (claims 1-16) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the claims in the application are closely related, requiring common areas of search. Thus, Applicant argues, there would be no benefit to restriction. This is not found persuasive because the nucleic acid of Group I can be used in many processes. Additionally, as the growth conditions of the methods of Groups II-IV are quite unrelated, there would not be common areas of search and consideration.

However, a search on Group I recovered prior art pertinent to Group II. Thus, as a courtesy to Applicant, Groups I and II have been rejoined. Claims 1-16 and 29-31 are examined.

Claims 32-37 are withdrawn from consideration as being drawn to nonelected inventions.

The requirement is still deemed proper and is therefore made FINAL.

2. The drawings are objected to for the reasons indicated on accompanying form PTO 948. Correction is required.

3. The title of the invention is not descriptive of the instant invention, as the instant invention is drawn to a gene encoding an elicitor, not to the elicitor itself. A new title is required that is clearly indicative of the invention to which the claims are directed. Note that titles can be up to 500 characters long.

Claim Rejections - 35 USC § 112

4. Claims 1-16 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:1 or encoding SEQ ID NO:2, does not reasonably provide enablement for nucleic acids that hybridize under conditions

of unspecified stringency to SEQ ID NO:1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to nucleic acids that hybridize under conditions of unspecified stringency to SEQ ID NO:1 and cells and plants transformed with those nucleic acids.

The instant specification, however, fails to provide guidance for which amino acids of SEQ ID NO:2 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain the activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

It cannot be predicted by one of skill in the art that nucleic acids that hybridize to SEQ ID NO:1 will encode a protein with the same activity as SEQ ID NO:2. Bowie et al (1990, Science 247:1306-10) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of the protein to fold into unique three-dimensional structures that allows it to function and carry out the instructions of the genome. The cited reference also teaches that the prediction of protein structure from sequence data and, in turn, utilizing predicted structural determinations to ascertain functional aspects of the protein, is extremely complex (pg 1306, left column). Bowie et al teach that while it is known that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three-

dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or none at all (pg 1306, right column).

The sensitivity of proteins to alterations in even a single amino acid in a sequence is exemplified by Lazar et al (1988, Mol. Cell. Biol. 8:1247-1252), who teach that a replacement of aspartic acid at position 47 with alanine or asparagine in transforming growth factor alpha had no effect, but that replacement with serine or glutamic acid sharply reduced biological activity (see the abstract). Small changes in amino acid sequence can completely modify enzymatic function; Broun et al (1998, Science 282:1315-1317) teach that a change of four amino acids converts an oleate 12-desaturase to a hydroxylase. Thus, Lazar et al and Broun et al demonstrated that one or few amino acid substitutions could dramatically affect the biological activity and the structure-function characteristics of a protein.

Making "conservative" substitutions (*e.g.*, substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Lazar et al (*supra*) showed that the "conservative" substitution of glutamic acid for aspartic acid at position 47 reduced biological function of transforming growth factor alpha while "nonconservative" substitutions with alanine or asparagine had no effect (abstract). Similarly, Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1). All these mutated proteins, however, would have at least 95% identity to the

original protein. The nucleic acids encoding all these mutated proteins, however, would hybridize under high stringency to the nucleic acids encoding the original protein.

A number of bacterial genes that encode proteins associated with the production of a hypersensitive response have been isolated from loss-of- hypersensitive-response mutants (He, 1996, Plant Physiol. 112:865-869, see pg 866, left column, paragraph 2 to right column, paragraph 2). Analysis of the biochemical functions of those proteins have shown that they include gene regulation proteins, secretion apparatus proteins, and secreted elicitors (pg 866, right column, paragraph 3, to pg 868, right column, paragraph 2).

The use of the genes encoding each type of hypersensitive response protein for imparting disease resistance in plants would have different requirements. The instant specification fails to provide guidance for each of these requirements and fails to teach the specific function of the instant gene.

Additionally, expression of *hrp* genes in plants is unpredictable. As constitutive elicitor production can be lethal to a plant, producing disease resistance via transformation with a gene encoding an elicitor protein also requires a pathogen-induced promoter (Keller et al, 1999, Plant Cell 11:223-235, see pg 224, left column paragraph 1). This is illustrated by Bauer et al (1999, Acta Hort. 489:301-304), who showed that while *Arabidopsis* plants transformed with the *hrpN* gene expressed behind a pathogen-inducible promoter were resistant to downy mildew, those transformed with the *hrpN* gene expressed behind a constitutive promoter were not (pg 302, paragraphs 5-6). In fact, constitutive expression of *hrpN* in these latter plants resulted in physical damage to the plants (pg 302, paragraph 6). Bauer et al also showed that the *hrpN* construct must be expressed with a signal sequence for export of the protein from the plants cells

production of resistant plants to be successful (pg 302, paragraph 5). The instant specification fails to teach the necessity for inducible promoters or how lethality or plant damage can be prevented without them, and it fails to teach the need for signal sequences for protein export.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids that hybridize under conditions of unspecified stringency to SEQ ID NO:1 and cells and plants transformed with those nucleic acids.

5. Claims 1-16 and 29-31 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA molecules that hybridize to SEQ ID NO:1 under conditions of unspecified stringency. In contrast, the specification only describes nucleic acids from *Erwinia amylovora* that comprise SEQ ID NO:1 or encode SEQ ID NO:2.

No description is provided as to the function of the encoded protein. While a sequence search suggested some homology of the protein of SEQ ID NO;2 with pectate lyases, as pointed out in the specification, the instant protein is missing a conserved cysteine and no pectate lyase activity was detected in the protein(pg 28, lines 28-30). The only known function is that the protein encoded by the instant nucleic acid is that it is a "hypersensitive response" protein. The actual functions of other hypersensitive response eliciting proteins appear to either in secretion or are unknown (Bonas, 1994, Current Topics in Micro. and Immol. 192:79-98, see paragraph

spanning pg 85-88, and pg 89). Collmer et al (1998, Methods Microbiol. 27:139-148) teach that the functions of secreted *hrp* proteins are unknown (pg 145, paragraph 2).

Homology alone is not sufficient to describe the structural features that distinguish a particular genes from other genes in an organism. As the activity of the instant protein is not described and as the instant specification fails to teach the structural features that distinguish hypersensitive response eliciting proteins from non hypersensitive response eliciting proteins, nucleic acids that hybridize to SEQ ID NO:1 are not described within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, and given the high level of unpredictability in this art, one skilled in the art would not have been in possession of the genus claimed at the time this application was filed.

See *University of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed, Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-16 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 1 and 4 are indefinite for their recitation of "a DNA molecule which hybridizes to a DNA molecule comprising a nucleotide sequence of SEQ ID No. 1 under stringent conditions" in part (c). It is not clear if "under stringent conditions" is intended to modify "SEQ ID No:1", "sequence" or "hybridizes". Additionally, it is not clear what level of stringency constitutes "stringent conditions". For purposes of examination, all levels were assumed. Such treatment does not relieve Applicant of the responsibility to respond to this rejection.

Claims 1(a), 1(c), 2 and 4 are indefinite in their recitation of "a DNA molecule comprising a nucleotide sequence of SEQ ID NO:21". It is not clear how many bases of SEQ ID NO:1 are part of "a nucleotide sequence". For purposes of examination, one base was assumed. If Applicant wishes to claim a DNA molecule of SEQ ID NO:1, the phrase should be replaced with --a DNA molecule of SEQ ID NO:1--. Such treatment does not relieve Applicant of the responsibility to respond to this rejection.

Claims 1 and 3 are indefinite in their recitation of "a DNA molecule encoding a protein comprising an amino acid of SEQ ID NO:2". It is not clear if Applicant really intended the protein to comprise only one amino acid of SEQ ID NO:2, and thus have the claim read on all protein-encoding DNA molecules (all have at least one amino acid in common with SEQ ID NO:2). For purposes of examination, that, however, was assumed. If Applicant wishes to claim a DNA molecule encoding a protein of SEQ ID NO:2, the phrase should be replaced with --a DNA molecule encoding a protein of SEQ ID NO:2--. Such treatment does not relieve Applicant of the responsibility to respond to this rejection.

Claim 7 is indefinite in its recitation of "is in proper sense orientation and correct reading frame". It is unclear what an improper sense orientation would be. Additionally, it is unclear relative to what the reading frame is correct.

Claims 1(d) and 5 are not written in proper Markush format. The claims should be in the format "selected from the group consisting of A, B, C and D." Alternately, the "and" after "(b)," should be replaced with --or--. See MPEP § 2173.05(h).

Claim 9 not written in proper Markush format. The claim should be in the format "selected from the group consisting of A, B, C **and** D." The "or" in line 2 should be replaced with --and--. See MPEP § 2173.05(h).

Claim 6 is indefinite for its recitation of "An expression vector transformed with the DNA molecule". As vectors are not transformed with DNA (only cells can be transformed), "transformed with" should be replaced with --comprising--.

Similarly, claim 10 is indefinite for its recitation of "wherein the DNA molecule is transformed with an expression vector." As DNA molecules are not transformed with expression vectors, "transformed with" should be replaced with --comprised within--.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

9. Claims 1-10 are rejected under 35 U.S.C. 102(a) as being anticipated by Kim et al (Phytopathology 87:S52).

Kim et al teach the *hrpW* gene from *E. amylovora*. If not identical to the instant gene, it would hybridize to SEQ ID NO:1 because it encodes a protein that has homology to pectate lyases. This nucleic acid is in an expression construct because the promoter has been identified and it would be in bacterial cells for purposes of molecular biological manipulation.

10. Claims 1-16 and 29-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bauer et al (US Patent 5,850,015, filed June, 1995).

Bauer et al teach the $hrpN_{Ech}$ gene from *E. chrysanthemi* and that was heterologously expressed in *E. amylovora* (column 19, line 11, to column 22, line 2). This nucleic acid was also

transformed into a wide variety of plants and used to impart disease resistance (claims 9-19). This nucleic acid encodes a hypersensitive response protein that would share at least an amino acid of SEQ ID NO:2; it would share at least a nucleotide with SEQ ID NO:1.

11. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wei et al (1992, Science 257:85-88).

Wei et al teach a hrp gene from *E. amylovora* (Fig. 1). This nucleic acid would be in bacterial cells for purposes of molecular biological manipulation. This nucleic acid encodes a hypersensitive response protein that would share at least an amino acid of SEQ ID NO:2; it would share at least a nucleotide with SEQ ID NO:1.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula K. Hutzell, can be reached on (703) 308-4310. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 or (703) 872-9306 for regular communications and (703) 308-4242 or (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, Dianeice Jacobs, at (703) 305-3388.

Anne R. Kubelik, Ph.D.
December 5, 2001

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PRIMARY EXAMINER
GROUP ~~180~~ 1638